Reaction of 3-Acetonyl-5-cyano-1,2,4-thiadiazole with Phenylhydrazine Hydrochlorides: Indolization and Phenylpyrazolation

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Treatment of 3-acetonyl-5-cyano-1,2,4-thiadiazole (1) with 4-methyl or 4-methoxyphenylhydrazine hydrochloride provided 5-cyano-3-(2,5-dimethylindol-3-yl)-1,2,4-thiadiazole (2) or 5-cyano-3-(5-methoxy-2-methylindol-3-yl)-1,2,4-thiadiazole (3) as the sole product, respectively. In contrast, treatment of 1 with phenylhydrazine hydrochloride resulted in the formation of 5-cyano-3-(2-methylindol-3-yl)-1,2,4-thiadiazole (4) and the unexpected 5-cyano-3-(3,5-dimethyl-1-phenylpyrazol-4-yl)-1,2,4-thiadiazole (5). In a similar manner, when 1 was treated with 4-chlorophenylhydrazine hydrochloride, indolization was suppressed by phenylpyrazolation giving rise to 5-cyano-3-(5-chloro-2-methylindol-3-yl)-1,2,4-thiadiazole (6) and 5-cyano-3-[1-(4-chlorophenyl)-3,5-dimethylpyrazol-4-yl]-1,2,4-thiadiazole (7). The reaction mechanism is discussed. Compounds 4, 5 and 6 exhibited weak antimicrobial activity against *Helicobacter pylor*i.

Key words 3-acetonyl-5-cyano-1,2,4-thiadiazole; phenylpyrazole; indole; phenylhydrazine hydrochloride; *Helicobacter pylori*

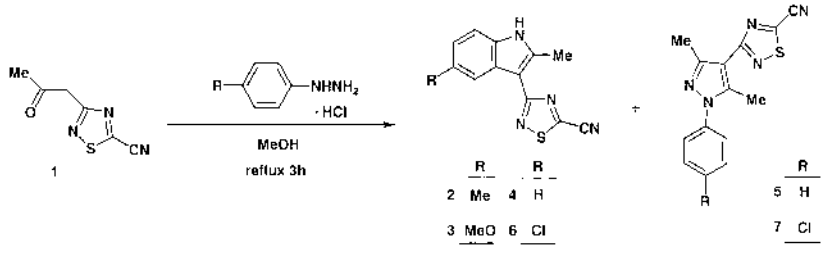
In a preceding paper,[1] we reported a new synthesis of 5-cyano-1,2,4-thiadiazoles using Appel's salt. In the course of studies on the chemical and biological aspects of 5-cyano-1,2,4-thiadiazole derivatives, our interest has been focused on using 3-acetonyl-5-cyano-1,2,4-thiadiazole (**1**) for synthesis of indole derivatives, due to their anticipated diverse range of biological activities.[2] We first examined the reaction of **1** with different phenylhydrazine hydrochlorides expecting the formation of indole analogs *via* Fischer indole synthesis,[3] but the unexpected formation of phenylpyrazole derivatives was encountered, being the subject of this paper.

Treatment of **1** with 4-methyl- or 4-methoxyphenylhydrazine hydrochloride afforded an indole analog, 5-cyano-3-(2,5-dimethylindol-3-yl)-1,2,4-thiadiazole (**2**) or 5-cyano-3-(5-methoxy-2-methylindol-3-yl)-1,2,4-thiadiazole (**3**), each as the sole product expected in 61.1% or 86.2% yield, respectively (Table 1, entries 1, 2). The structures of **2** and **3** were substantiated on the basis of elemental analysis and IR and NMR spectral data. However, when **1** was allowed to react with phenylhydrazine hydrochloride, the expected 5-cyano-3-(2-methylindol-3-yl)-1,2,4-thiadiazole (**4**) was obtained in a lower yield (13.9%), while the unexpected 5-cyano-3-(3,5-dimethyl-1-phenylpyrazol-4-yl)-1,2,4-thiadiazole (**5**) was found to be the main product (39.6%) (Table 1, entry 3). The structure of **5** was determined by single crystal X-ray analysis (Experimental), and a perspective drawing of the molecular structure is shown in Fig. 1.

A similar result was obtained for treatment of **1** with 4-chlorophenylhydrazine hydrochloride, that is, 5-cyano-3-(5-chloro-2-methylindol-3-yl)-1,2,4-thiadiazole (**6**) was obtained in an 8.0% yield, whereas a phenylpyrazole derivative, 5-cyano-3-[1-(4-chlorophenyl)-3,5-dimethylpyrazol-4-yl]-1,2,4-thiadiazole (**7**) was formed in a 35.0% yield (Table 1, entry 4). The structure of **7** was elucidated based on elemental analysis and spectral data in comparison with those of **5**.

Regarding the reaction mechanism giving rise to phenylpyrazole as well as indole derivatives (Fischer indole synthesis), the following pathways seem viable. Thus, in acidic medium, the reaction was initiated by attack of phenylhydrazine on the carbonyl moiety of **1** to afford a phenylhydrazone (**i**),[3] and Fischer indole synthesis would follow (*via* route a). The indolization was promoted by the electron-donating properties of substituents (alkyl, alkoxy) in the phenyl ring of the phenylhydrazone moieties. On the other hand, electron-attracting groups (NO_2, CN, COOH, halogens) in the phenylhydrazone part would retard the cy-

Table 1



Entry	R	Yield (%) (Compd. No.)	
1	Me	61.1 (**2**)	—
2	MeO	86.2 (**3**)	—
3	H	13.9 (**4**)	39.6 (**5**)
4	Cl	8.0 (**6**)	35.0 (**7**)

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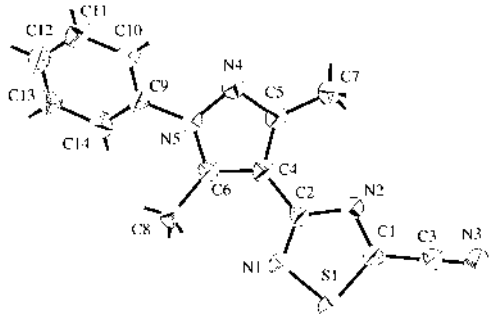

Selected bond lengths (Å), bond angles (°) and torsion angles (°) of **5**

Bond lengths			Bond angles				Bond angles				
S(1)	N(1)	1.636 (2)	N(1)	S(1)	C(1)	91.7 (1)	C(2)	C(4)	C(5)	127.6 (2)	
S(1)	C(1)	1.693 (2)	S(1)	N(1)	C(2)	109.5 (2)	C(2)	C(4)	C(6)	126.9 (2)	
N(1)	C(2)	1.321 (3)	C(1)	N(2)	C(2)	108.3 (2)	C(5)	C(4)	C(6)	105.3 (2)	
N(2)	C(1)	1.313 (3)	N(5)	N(4)	C(5)	104.9 (2)	N(4)	C(5)	C(4)	111.1 (2)	
N(2)	C(2)	1.369 (3)	N(4)	N(5)	C(6)	112.9 (2)	N(4)	C(5)	C(7)	119.8 (2)	
N(3)	C(3)	1.137 (3)	N(4)	N(5)	C(9)	118.2 (2)	C(4)	C(5)	C(7)	129.1 (2)	
N(4)	N(5)	1.368 (3)	C(6)	N(5)	C(9)	128.9 (2)	N(5)	C(6)	C(4)	105.8 (2)	
N(4)	C(5)	1.316 (3)	S(1)	C(1)	N(2)	113.1 (2)	N(5)	C(6)	C(8)	124.0 (2)	
N(5)	C(6)	1.345 (3)	S(1)	C(1)	C(3)	126.1 (2)	C(4)	C(6)	C(8)	130.2 (2)	
N(5)	C(9)	1.434 (3)	N(2)	C(1)	C(3)	120.7 (2)	Torsion angles				
C(1)	C(3)	1.423 (3)	N(1)	C(2)	N(2)	117.4 (2)	N(2)	C(2)	C(4)	C(5)	6.6 (3)
C(2)	C(4)	1.448 (3)	N(1)	C(2)	C(4)	122.0 (2)	N(1)	C(2)	C(4)	C(6)	3.2 (4)
C(4)	C(5)	1.417 (3)	N(2)	C(2)	C(4)	120.5 (2)	N(4)	N(5)	C(9)	C(10)	−49.3 (3)
C(4)	C(6)	1.389 (3)	N(3)	C(3)	C(1)	178.8 (3)	C(6)	N(5)	C(9)	C(14)	−48.7 (3)

Fig. 1. ORTEP Drawing of **5**

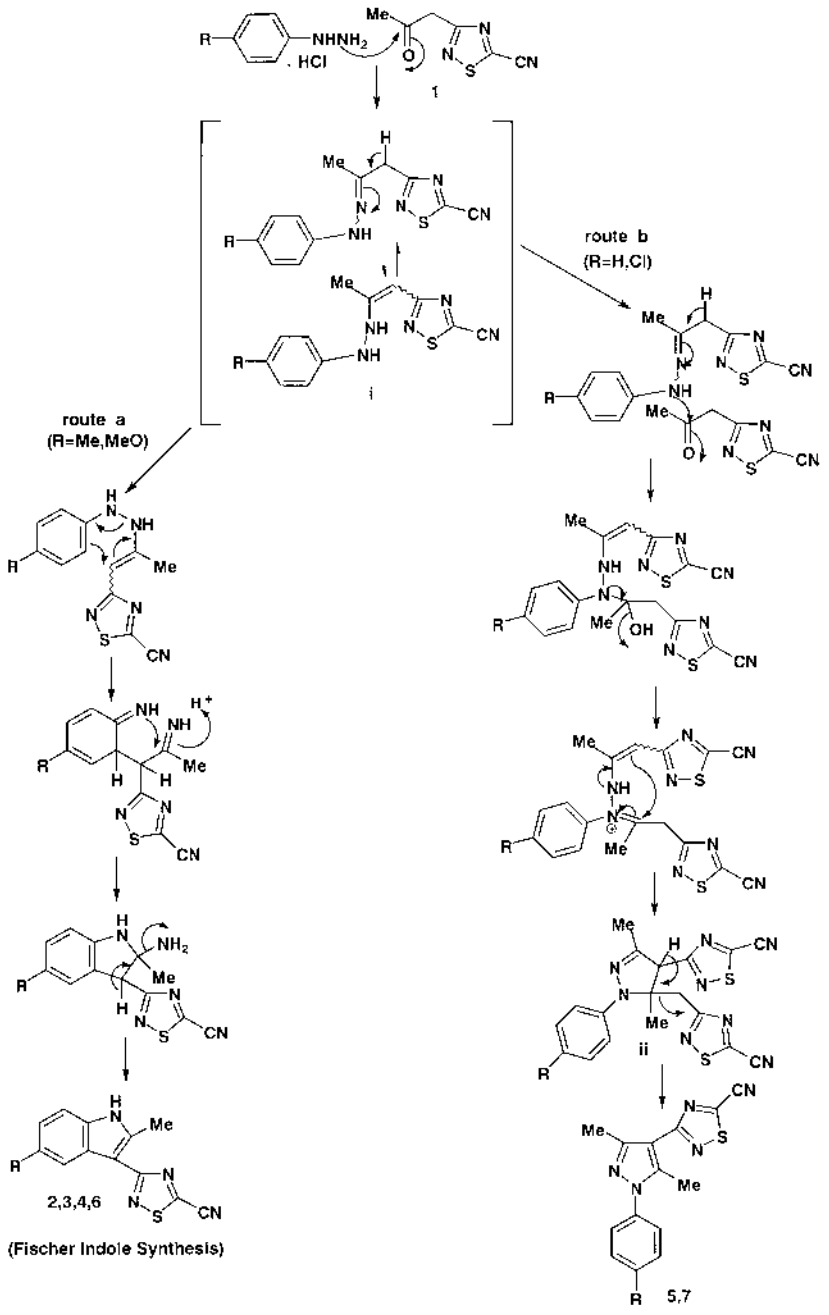

Chart 1

clization leading to indoles,[4] and would instead favor phenylpyrazole formation. The presumable mechanism of formation of both indole and phenylpyrazole analogs may be summarized in the following manner (Chart 1). The formations of both indole and phenylpyrazole are initiated by phenylhydrazone (**i**). When the substituent in the phenyl ring (R) is electron donating, [3, 3] sigmatropic rearrangement predominates to yield an indole (Fischer indole synthesis, route a). When R is H or Cl, a phenylpyrazole formation (route b) may be favored over the indole formation (route a). Although a number of syntheses of pyrazole and pyrazoline ring constructions using hydrazines as their precursors have been performed, their reaction mechanisms are not yet fully characterized, except for a proposal by Chapelle *et al*.[5] on the mechanism of formation of pyrazolines, which suggests reaction initiation by a hydrazine and two carbonyl compounds.[5] Taking advantage of the proposal by Chapelle *et al.*, our present finding providing phenylpyrazole compounds (**5**, **7**) may be explained as shown in Chart 1. Thus, under the reaction conditions employed, phenylpyrazoline compound (**i i**) formed may be readily aromatized to provide phenylpyrazole compounds (**5**, **7**). Attempts to isolate the phenylpyrazoline intermediate have so far been unsuccessful. In conclusion, we have found that the reaction products of **1** with phenylhydrazine hydrochlorides vary depending upon the property of substituent(R) in phenylhydrazine hydrochlorides. When R is an electron donating group (Me, MeO), an indole formation (products **2**, **3**) predominates, whereas when it is H or Cl, unexpected phenylpyrazole formation (products **5**, **7**) is favored over the indolization (products **4**, **6**). Among compounds **2**—**6** tested for various antimicrobial activities, compounds **4**, **5** and **6** showed only weak activities against *Helicobacter pylori* (SS1, ATCC 43504, ATCC 43629, SR-9043 strains) (MIC 62.5 μg/ml).[6]

Experimental

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken with a JEOL JNM-GSX 270 and a JEOL JNM A-400 spectrometer, respectively. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane, and the coupling constants are in Hz. Silica gel column chromatography was carried out using Kieselgel 60 (70—230 mesh, Merck).

General Procedure for the Reaction of 3-Acetonyl-5-cyano-1,2,4-thiadiazole (1) with Phenylhydrazine Hydrochloride Phenylhydrazine hydrochloride (520 mg, 3.6 mmol) was added to a solution of 3-acetonyl-5-cyano-1,2,4-thiadiazole (**1**) (600 mg, 3.6 mmol) in dry MeOH (18 ml) under dry nitrogen and the resulting mixture was refluxed for 3 h. After removal of MeOH, the residue was dissolved in CH_2Cl_2 and the solution was washed with brine. The organic layer was dried over Na_2SO_4, then the solvent was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt=3 : 1) to give **4** (120 mg 13.9%) and **5** (200 mg, 39.6%).

X-Ray Crystallographic Analysis of 5 Crystals of **5** were grown from *n*-hexane/ethyl acetate as colorless prisms. A crystal of approximate dimensions 0.2×0.2×0.4 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Mo-K_α radiation and a rotating anode generator. Of the 2554 reflections (2θ<49.1°) which were collected, 2408 were unique. Crystal data: $C_{14}H_{11}N_5S$, M.W.=281.33; monoclinic, space group $P2_1/c$, a=10.039(3) Å, b=7.891(4) Å, c=17.213(3) Å, β=101.84(2)°, V=1334.5(8) Å^3, Z=4, D_c=1.40 g/cm^3, F_{000}=584.00, λ=0.71069 Å.

Structure Solution and Refinement: The structure was solved by a direct method using SAPI91. The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, the rest were included in fixed positions. The final cycle of full-matrix least-squares refinement was based on 1879 observed reflections [$I>2\sigma(I)$]. The final R value was 0.039.

5-Cyano-3-(2,5-dimethylindol-3-yl)-1,2,4-thiadiazole (2) Yellowish fine crystals. mp 182—184 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.87 (3H, s), 7.09 (1H, d, J=7.6 Hz), 7.24 (1H, d, J=7.6 Hz), 8.20 (1H, br s), 8.25 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.7 (q), 21.7 (q), 106.0 (s), 110.1 (d), 111.2 (s), 120.8 (d), 124.2 (d), 127.0 (s), 131.2 (s), 133.1 (s), 140.2 (s), 155.7 (s), 172.5 (s). IR (KBr) cm^{-1}: 3377, 2240, 1560, 1487, 1459, 1225, 1137. EI-MS *m/z* (rel. int. %): 254 (M^+, 97), 202 (21), 169 (100), 115 (12), 53 (21), 32 (20). *Anal*. Calcd for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03; S, 12.61. Found: C, 61.11; H, 4.10; N, 21.77; S, 12.56.

5-Cyano-3-(5-methoxy-2-methylindol-3-yl)-1,2,4-thiadiazole (3) Yellowish fine crystals. mp 140—141 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.86 (3H, s), 3.92 (3H, s), 6.89 (1H, dd, J=2.4, 8.6 Hz), 7.23 (1H, d, J=8.6 Hz), 7.96 (1H, d, J=2.4 Hz), 8.22 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 14.7 (q), 55.9 (q), 103.4 (d), 106.2 (s), 111.2 (d), 112.4 (d), 127.5 (s, 2C), 129.7 (s), 140.7 (s), 155.5 (s), 155.6 (s), 172.4 (s). IR (KBr) cm^{-1}: 3389, 2239, 1557, 1485, 1461, 1201, 1165. EI-MS *m/z* (rel. int. %): 270 (M^+, 100), 255 (53), 227 (35), 143 (34), 53 (14). *Anal.* Calcd for $C_{13}H_{10}N_4OS$: C, 57.76; H, 3.73; N, 20.73; S, 11.86. Found: C, 57.77; H, 3.82; N, 20.55; S, 11.80.

5-Cyano-3-(2-methylindol-3-yl)-1,2,4-thiadiazole (4) Yellowish fine crystals. mp 177—178 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s), 7.24—7.31 (2H, m), 7.35—7.38 (1H, m), 8.29 (1H, br s), 8.46 (1H, dd, J=2.4, 6.4 Hz). IR (KBr) cm^{-1}: 3355, 2245, 1556, 1492, 1217, 751. EI-MS *m/z* (rel. int. %): 240 (M^+, 82), 188 (34), 155 (100), 128 (18), 101 (20). *Anal.* Calcd for $C_{12}H_8N_4S$: C, 59.98; H, 3.36; N, 23.32. Found: C, 59.60; H, 3.49; N, 22.97.

5-Cyano-3-(3,5-dimethyl-1-phenylpyrazol-4-yl)-1,2,4-thiadiazole (5) Colorless crystals. mp 118—121 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 2.67 (3H, s), 7.43—7.54 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.0 (q), 14.5 (q), 110.8 (s), 112.1 (s), 125.6 (d, 2C), 128.4 (d), 129.2 (d, 2C), 138.9 (s), 141.9 (s), 150.0 (s), 156.4 (s), 170.8 (s). IR (KBr) cm^{-1}: 2926, 2236, 1561, 1506, 1434, 1139, 1111, 757, 689. EI-MS *m/z* (rel. int. %): 281 (M^+, 100), 229 (13), 196 (25), 77 (78), 51 (55). *Anal.* Calcd for $C_{14}H_{11}N_5S$: C, 59.77; H, 3.94; N, 24.89. Found: C, 59.43; H, 4.09; N, 24.56.

5-Cyano-3-(5-chloro-2-methylindol-3-yl)-1,2,4-thiadiazole (6) Yellowish fine crystals. mp 193—195 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.89 (3H, s), 7.20 (1H, dd, J=1.8, 7.7 Hz), 7.27 (1H, d, J=7.7 Hz), 8.32 (1H, br s), 8.46 (1H, d, J=1.8 Hz). IR (KBr) cm^{-1}: 3363, 2245, 1558, 1485, 1463, 1211, 758. EI-MS *m/z* (rel. int. %): 274 (M^+, 100), 239 (80), 222 (23), 189 (67), 127 (16). *Anal.* Calcd for $C_{12}H_7ClN_4S$: C, 52.45; H, 2.57; N, 20.39. Found: C, 52.61; H, 2.73; N, 20.21.

5-Cyano-3-[1-(4-chlorophenyl)-3,5-dimethylpyrazol-4-yl]-1,2,4-thiadiazole (7) Colorless fine crystals. mp 155—157 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 2.66 (3H, s), 7.41 (2H, d, J=8.9 Hz), 7.48 (2H, d, J=8.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 12.9 (q), 14.4 (q), 110.7 (s), 112.4 (s), 126.7 (d, 2C), 129.4 (d, 2C), 134.2 (s), 137.4 (s), 141.8 (s), 150.3 (s), 156.5 (s), 170.4 (s). IR (KBr) cm^{-1}: 2969, 2241, 1564, 1500, 1439, 1142, 1092, 830. EI-MS *m/z* (rel. int. %): 315(M^+, 100), 280 (10), 263 (15), 230 (18), 111 (55), 75 (55). *Anal.* Calcd for $C_{14}H_{10}ClN_5S$: C, 53.24; H, 3.19; N, 22.18; Cl,11.22; S, 10.15. Found: C, 53.15; H, 3.27; N, 21.98; Cl, 11.34; S, 10.13.

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References and Notes

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